

ONLINE SEARCH REQUEST FORM

USER Toni ScheinerSERIAL NUMBER 08/083590ART UNIT 1806PHONE 308-3983DATE 10/30/95

Please give a detailed statement of requirements. Describe as specifically as possible the subject matter to be searched. Define any terms that may have special meaning. Give examples or relevant citations, authors, or keywords, if known.

You may include a copy of the broadest and or relevant claim(s).

Please search SEQ ID NOS:

5 thru 21

FOR OFFICIAL USE

4/30/92

XCS Service v1.00
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08/083590 10/24/95

Artavanis - Tsakonas
Fehon
Zagouras
Blau mueller

Set Items Description

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Set	Items	Description
S1	254	NOTCH(W)PROTEIN?
S2	123	RD S1 (unique items)
S3	486109	METASTA?
S4	2173554	CANCER OR CARCINOMA
S5	123	S1 AND (S2 OR S3)
S6	8	S2 AND (S3 OR S4)

955 012

879 038

659 189

791 923

SYSTEM:OS - DIALOG OneSearch

File 5:BIOSIS PREVIEWS(R) 1969-1995/Oct W4

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*File 5: s (Meeting()Abstract) or abstracts/DE for 1994+ conference records

File 73:EMBASE 1974-1995/Iss 41

(c) 1995 Elsevier Science B.V.

File 76:Life Sciences Collection 1978-1995/Aug

(c) 1995 Cambridge Sci Abs

File 125:CLAIMS(R)/US PATENT JUL 1995/OCT 17 (c) 1995 IFI/Plenum Data Corp

File 144:Pascal 1973-1995/Sep

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File 348:EUROPEAN PATENTS 1978-1995/OCT W2

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*File 348: Fulltext is forthcoming. See HELP NEWS 348 for more information.

File 350:Derwent World Pat. 1963-1980/UD = 9540

(c) 1995 Derwent Info Ltd

File 351:DERWENT WPI 1981-1995/UD = 9541;UA = 9535;UM = 9530

(c)1995 Derwent Info Ltd

File 357:Derwent Biotechnology Abs 1982-1995/Oct B2
 (c) 1995 Derwent Publ Ltd
 File 358:Current Biotech Abs 1983-1995/Sep
 (c) 1995 Royal Society of Chemistry
 *File 358: May 1995 update is in process and should complete later
 today (09 Jun 1995). Subsequent updates should be back on schedule.
 File 377:Derwent Drug File 1983-1995/Oct W3
 (c) 1995 Derwent Info Ltd.
 File 399:CA SEARCH(R) 1967-1995/UD = 12317
 (c) 1995 American Chemical Society
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 File 434:SciSearch(R) 1974-1995/Oct W1
 (c) 1995 Inst for Sci Info
 File 442:AMA Online Journal 1982-1995/Aug W4
 (c) 1995 American Medical Assoc.
 *File 442: AMA Journals Online updates weekly beginning with UD = 9504W3.
 File 444:NEJM Online 1985-1995/Sep W4
 (c) 1995 New England Journal of Medicine.
 File 456:NME Express 1992-1995/Sep B1
 (c) 1995 J.R. Prous, S.A.
 File 624:McGraw-Hill Publications Onl. 1985-1995/Oct 19
 (c) 1995 McGraw-Hill
 *File 624: Please type 'E JN =' for all current journals available.

6/7/1 (Item 1 from file: 5)
 DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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11066516 BIOSIS Number: 97266516

Ep-CAM: A human epithelial antigen is a homophilic cell-cell adhesion molecule

Litvinov S V; Velders M P; Bakker H A M; Fleuren G J; Warnaar S O
 Dep. Pathol., State Univ. Leiden, Wassenaarsweg 62, P.O. Box 9603, 2300
 RC Leiden, NET

Journal of Cell Biology 125 (2). 1994. 437-446.

Full Journal Title: Journal of Cell Biology

ISSN: 0021-9525

Language: ENGLISH

Print Number: Biological Abstracts Vol. 097 Iss. 012 Ref. 168066

The epithelial glycoprotein 40 (EGP40, also known as GA733-2, ESA, KSA, and the 17-1A antigen), encoded by the GA-733-2 gene, is expressed on the baso-lateral cell surface in most human simple epithelia. The protein is also expressed in the vast majority of carcinomas and has attracted attention as a tumor marker. The function of the protein is unknown. We demonstrate here that EGP40 is an epithelium-specific intercellular adhesion molecule. The molecule mediates, in a Ca-2+ -independent manner, a

homophilic cell-cell adhesion of murine cells transfected with the complete EGP40 cDNA. Two murine cell lines were tested for the effects of EGP40 expression: fibroblastic L cells and dedifferentiated mammary carcinoma L153S cells. The expression of the EGP40 protein causes morphological changes in cultures of transfected cells-increasing intercellular adhesion of the transfectants-and has a clear effect on cell aggregating behavior in suspension aggregation assays. EGP40 directs sorting in mixed cell populations, in particular, causes segregation of the transfectants from the corresponding parental cells. EGP40 expression suppresses invasive colony growth of L cells in EHS-matrigel providing tight adhesions between cells in growing colonies. EGP40 can thus be considered a new member of the intercellular adhesion molecules. In its biological behavior EGP40 resembles to some extent the molecules of the immunoglobulin superfamily of cell adhesion molecules (CAMs), although no immunoglobulin-like repeats are present in the EGP40 molecule. Certain structural similarities in general organization of the molecule exist between EGP40 and the lin-12/Notch proteins. A possible role of this adhesion molecule in formation of architecture of epithelial tissues is discussed. To reflect the function of the molecule the name Ep-CAM for EGP40 seems appropriate.

6/7/2 (Item 1 from file: 76)
DIALOG(R)File 76:Life Sciences Collection
(c) 1995 Cambridge Sci Abs. All rts. reserv.

2058692 82003754879

Alterations in Notch signaling in neoplastic lesions of the human cervix
Zagouras, P.; Stifani, S.; Blaumueller, C.M.; Carcangiu, M.L.;
Artavanis-Tsakonas, S.

Dep. Biol., Yale Univ., New Haven, CT 06536, USA

PROC. NATL. ACAD. SCI. USA; 92(14), pp. 6414-6418 1995

Language: English Summary Language: English

Document Type: Journal article

Subfile: 26 Oncogenes Abstracts; 07 Genetics Abstracts

The development of cancer is a cellular process that reflects and is partly driven by alterations in cell determination. Mutations in various molecules responsible for cell determination have been identified as being oncogenic, but little is known about the involvement of normal cell fate-determining mechanisms in the oncogenic process. The Notch pathway defines an evolutionarily conserved, general cell interaction mechanism that controls fundamental aspects of cell determination during vertebrate and invertebrate development. We have explored the involvement of the human Notch pathway in human cervical tissues, which define a cellular environment where cell fate changes take place and where neoplastic conditions have been well characterized. Our evidence suggests that Notch expression is associated with cell populations that are undergoing cell fate changes and that Notch activity can be used to monitor cell fate abnormalities in cervical as well as other epithelial neoplasias.

6/7/3 (Item 1 from file: 351)
DIALOG(R)File 351:DERWENT WPI
(c)1995 Derwent Info Ltd. All rts. reserv.

010367905 WPI Acc No: 95-269267/35

XRAM Acc No: C95-122052

XRPX Acc No: N95-207033

Novel deltex protein and related nucleic acids and antibodies - useful
in treating/diagnosing a malignancy characterised in aberrant level of
Notch-deltex protein binding activity, e.g. cancer

Patent Assignee: (UYYA) UNIV YALE

Author (Inventor): ARTAVANIS-TSAKONAS S; BUSSEAU I; DIEDERICH R J; MATSUNO
K; XU T

Number of Patents: 001

Number of Countries: 058

Patent Family:

CC Number	Kind	Date	Week
WO 9519779	A1	950727	9535 (Basic)

Priority Data (CC No Date): US 185432 (940121)

Applications (CC,No,Date): WO 95US825 (950120)

Language: English

EP and/or WO Cited Patents: 6.Jnl.Ref; WO 8912690; WO 9219734

Designated States

(National): AM; AU; BB; BG; BR; BY; CA; CN; CZ; EE; FI; GE; HU; JP; KE; KG
; KR; KZ; LK; LR; LT; LV; MD; MG; MN; MW; MX; NO; NZ; PL; RO; RU; SD;
SI; SK; TJ; TT; UA; UZ; VN

(Regional): AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; KE; LU; MC; MW; NL
; OA; PT; SD; SE; SZ

Abstract (Basic): WO 9519779 A

A substantially purified deltex protein is claimed. Also claimed are: (a) a protein comprising a fragment of a deltex protein, the fragment characterised in that it comprises: (i) 10, pref. 20 amino acids of the deltex protein; (ii) a Glu-rich cluster of the deltex protein; (iii) a fragment which binds to a Notch protein or to a mol, comprising the cdc 10/SW16/ankyrin repeats of a Notch protein; (iv) a first fragment which binds to a second deltex protein or to a mol. comprising a fragment of a second deltex protein; (v) a SH3 binding domain of the deltex protein; (2) a fragment of a deltex protein consisting of 10 continuous amino acids of a deltex protein, which displays one or more functional activities associated with a full length deltex protein; (3) a chimeric protein comprising a functionally active fragment of a deltex protein joined via a peptide bond to an amino acid sequence of a protein other than a deltex protein; (4) a peptide with 10-35 amino acids of a deltex protein sequence; (5) an antibody (Ab) which binds to a deltex protein; (6) a nucleic acid (I) and a nucleic acid (II) hybridisable to (I) in a high or low stringency conditions, where (I) encodes a deltex protein; (7) a nucleic acid encoding the protein of (1) to (3); (8) a nucleic acid vector comprising (I), (9) a recombinant cell contg. the nucleic acid vector

of (8); (10) an isolated oligonucleotide consisting of 6 nucleotides, comprising a sequence complementary to at least a portion of an RNA transcript of a deltex gene, and is hybridisable to the RNA transcript.

USE - The proteins, nucleic acids and Abs are used in pharmaceutical compsns, for treating or preventing a disease or disorder where function of a deltex protein is antagonised. The disease or disorder is a malignancy characterised by increased Notch activity, increased expression of a Notch protein or of a Notch deriv. capable of being bound by an anti-Notch Ab. Pref. the disease/disorder is cervical, breast or colon cancer. The malignancy may be a melanoma, seminoma or lung cancer. Antisense oligonucleotides are useful for treating patients with tumours. The deltex protein can also be used in diagnosis of a disease/disorder characterised by an aberrant level of Notch-deltex protein binding activity in a patient (claimed).

Dwg.0/17

Derwent Class: B04; D16; S03;

Int Pat Class: A61K-035/12; C07H-017/00; C07K-001/00; C07K-014/00;
C07K-016/00; C12N-001/00; C12N-005/00; C12N-015/00; C12Q-001/68;
G01N-033/53

6/7/4 (Item 2 from file: 351)
DIALOG(R)File 351:DERWENT WPI
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009855324 WPI Acc No: 94-135180/16

XRAM Acc No: C94-062475

XRPX Acc No: N94-106287

Notch protein and nuclear acid compositions - is used for treatment of disorders of cell fate or differentiation esp. breast, colon or cervical cancer

Patent Assignee: (UYYA) UNIV YALE

Author (Inventor): ARTAVANIS-TSAKONAS S; BLAUMUELLER C M; FEHON R G;
ZAGOURAS P

Number of Patents: 003

Number of Countries: 046

Patent Family:

CC Number	Kind	Date	Week	
WO 9407474	A1	940414	9416	(Basic)
AU 9453503	A	940426	9432	
EP 662827	A1	950719	9533	

Priority Data (CC No Date): US 83590 (930625); US 955012 (920930)

Applications (CC,No,Date): EP 93923752 (930930); WO 93US9338 (930930); WO 93US9338 (930930); AU 9453503 (930930)

Language: English

EP and/or WO Cited Patents: 6.Jnl.Ref; US 5115096; US 5132212; US 5264557

Designated States

(National): AU; BB; BG; BR; BY; CA; CZ; FI; HU; JP; KP; KZ; LK; LV; MG; MN

; MW; NO; NZ; PL; RO; RU; SD; SK; UA; US; UZ; VN
(Regional): AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT
; SE; OA

Filing Details: EP0662827 Based on WO 9407474; AU9453503 Based on WO 9407474

Abstract (Basic): WO 9407474 A

The pharmaceutical compsn. comprises a therapeutically effective amt. of a Notch protein (A) and a pharmaceutically acceptable carrier.

USE - The compsns. can be used for treatment of disorders of cell fats or differentiation. The therapeutic compsns. include Notch proteins and analogues, derivs. and fragments, antibodies, nucleic acid encoding, analogues and derivs., Notch antisense nucleic acids, toporythmic proteins and derivs. which bind or interact with Notch proteins, their encoding nucleic acids or Abs. The compsn. is pref. admin. to a cancerous condition, e.g. breast, colon or cervical cancer, or to prevent progression from a pre-neoplastic or non-malignant state into a neoplastic or malignant state. Dwg.0/17

Derwent Class: B04; D16; S03;

Int Pat Class: A61K-031/70; A61K-037/02; A61K-039/395; A61K-039/44; C07H-021/04; G01N-033/53; G01N-033/68

6/7/5 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
(c) 1995 Derwent Publ Ltd. All rts. reserv.

185234 DBA Accession No.: 95-12055 PATENT

Novel deltex protein and related nucleic acids and antibodies - antisense oligonucleotide application in cancer therapy and recombinant protein application in tumor diagnosis

AUTHOR: Artavanis-Tsakonas S; Busseau I; Diederich R J; Matsuno K

PATENT ASSIGNEE: Univ.Yale 1995

PATENT NUMBER: WO 9519779 PATENT DATE: 950727 WPI ACCESSION NO.: 95-269267 (9535)

PRIORITY APPLIC. NO.: US 185432 APPLIC. DATE: 940121

NATIONAL APPLIC. NO.: WO 95US825 APPLIC. DATE: 950120

LANGUAGE: English

ABSTRACT: A pure deltex protein (I) is claimed. Also claimed are: a fragment of (I) comprising at least 10 (preferably 20) amino acids of (I), a Glu-rich cluster of (I), a fragment which binds to a Notch protein or to a molecule comprising the cdc10/SW16/ankyrin repeats of a Notch protein, a fragment which binds to a second (I) or to a molecule comprising a fragment of a 2nd (I) and a SH3 binding domain of (I); (I) fragments having activity associated with full-length (I); a (I) fusion protein; a peptide of 3-10 amino acids of (I); an antibody binding (I); nucleic acid encoding (I) and nucleic acid hybridizing with this nucleic acid; a transformed cell containing vector plasmid pCaSpeR-hs-dx (ATCC 75640) encoding (I); and an isolated antisense oligonucleotide of at least 6 nucleotides comprising a sequence complementary to at least part of an RNA transcript of a (I) gene and

hybridizing with the RNA transcript. The proteins, nucleic acids and antibodies are used for melanoma, seminoma, lung carcinoma, mamma carcinoma, cervix carcinoma and colon carcinoma therapy and the proteins are used in diagnosis. (153pp)

6/7/6 (Item 2 from file: 357)

DIALOG(R)File 357:Derwent Biotechnology Abs

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164909 DBA Accession No.: 94-07460 PATENT

Notch protein and antisense DNA - application in carcinoma diagnosis, therapy and gene therapy

PATENT ASSIGNEE: Univ.Yale 1994

PATENT NUMBER: WO 9407474 PATENT DATE: 940414 WPI ACCESSION NO.: 94-135180 (9416)

PRIORITY APPLIC. NO.: US 83590 APPLIC. DATE: 930625

NATIONAL APPLIC. NO.: WO 93US9338 APPLIC. DATE: 930930

LANGUAGE: English

ABSTRACT: A pharmaceutical composition comprising a Notch protein (A) and a carrier is claimed. More specifically, the composition comprises a human Notch protein encoded by a specified DNA sequence which is bound by an antibody to a Notch protein. The following are also claimed: (1) a pure human Notch protein homolog of specified protein sequence; (2) nucleic acid encoding the protein of (1); (3) a recombinant cell containing the nucleic acid of (2); (4) a composition comprising a Notch protein or derivative (e.g. chimeric protein); (5) a composition comprising a molecule which antagonizes the function of a Notch protein; and (6) the use of the composition of (5) for treatment of cervix carcinoma, mamma carcinoma or colon carcinoma. In (4), the chimeric protein may include functionally active portions of the Notch protein encoded by human cDNA contained in plasmid pHN3k (ATCC 68609) and plasmid pHN5k (ATCC 68611). The therapeutic composition includes Notch proteins and analogs, antibodies, nucleic acid encoding the analogs, antisense nucleic acids, etc. which bind and interact with Notch proteins, their encoding nucleic acids or antibodies. (232pp)

6/7/7 (Item 1 from file: 358)

DIALOG(R)File 358:Current Biotech Abs

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074382 CBA Acc. No.: 13-09-007173 DOC. TYPE: Patent

Therapeutic and diagnostic method and compositions based on Notch proteins and nucleic acids.

AUTHOR: Artavanis-Tsakonas, S.; Fehon, R. G.; Zagouras, P.; Blaumeuller, C. M.

CORPORATE SOURCE: Yale Univ., New Haven, CT 06520, USA

CODEN: PIXXD2

PATENT NUMBER: WO 9407474

PATENT APPLICATION: US 955012 (920930)

PUBLICATION DATE: 14 Apr 1994 (940414) LANGUAGE: English

ABSTRACT: Therapeutic and diagnostic methods and compositions based on Notch proteins and nucleic acids are disclosed, together with the sequences of human Notch DNA and the encoded Notch protein. Disorders of cell fate or differentiation are treated by administering the Notch proteins, antibodies thereto, nucleic acids encoding the Notch proteins, antisense Notch nucleic acids, and toporhythmic proteins and derivatives which bind to or interact with Notch proteins. The methods are especially useful in cancer therapy.

6/7/8 (Item 1 from file: 434)

DIALOG(R)File 434:SciSearch(R)

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12122068 Genuine Article#: KN533 Number of References: 33

Title: DLK, A PUTATIVE MAMMALIAN HOMEOTIC GENE DIFFERENTIALLY EXPRESSED IN SMALL-CELL LUNG-CARCINOMA AND NEUROENDOCRINE TUMOR-CELL LINE

Author(s): LABORDA J; SAUSVILLE EA; HOFFMAN T; NOTARIO V

Corporate Source: US FDA,CTR BIOLOG & RES,8800 ROCKVILLE PIKE,BLDG

29/BETHESDA//MD/20892; US FDA,CTR BIOLOG EVALUAT &

RES/BETHESDA//MD/20892; GEORGETOWN UNIV,DEPT MED,DIV MED

ONCOL/WASHINGTON//DC/20007; GEORGETOWN UNIV,LOMBARDI CANC CTR,DEPT RADIAT MED/WASHINGTON//DC/20007

Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, 1993, V268, N6 (FEB 25), P 3817-3820

ISSN: 0021-9258

Language: ENGLISH Document Type: NOTE

Abstract: Gastrin releasing peptide is mitogenic for mouse Swiss 3T3 fibroblasts and certain human small cell lung carcinoma (SCLC) cells but not for mouse Balb/c 3T3 fibroblasts. To identify new molecules associated with the gastrin releasing peptide-responsive phenotype, clones isolated from a differential cDNA library between Swiss and Balb/c 3T3 fibroblasts were used to screen for their expression in human SCLC cell lines. Using this approach, we have isolated and characterized human and mouse cDNA clones encoding a novel protein. This protein is a putative transmembrane protein belonging to the epidermal growth factor-like superfamily. In vitro transcription and translation studies detect a 42-kDa protein, in agreement with the size predicted from the translated cDNA sequence. This protein (termed Delta-like or dlk) is highly homologous to invertebrate homeotic proteins, including Delta, and Notch, the products of neurogenic loci involved in normal neural differentiation in Drosophila. dlk is expressed in tumors with neuroendocrine features, such as neuroblastoma, pheochromocytoma, and a subset of SCLC cell lines. However, its expression in normal tissues is restricted to the adrenal gland and placenta. These data suggest that dlk may be involved in neuroendocrine differentiation and, because of its cellular location and restricted expression in normal tissues, it may be a potential

therapeutic target in neuroendocrine tumors, particularly SCLC.
?ads

QH573.C38

Cell 66(4) Aug 91
649-61

11/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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11026507 BIOSIS Number: 97226507

The level of cervical lymph node metastases: Their prognostic relevance and relationship with head and neck squamous carcinoma primary sites

Jones A S; Roland N J; Field J K; Phillips D E

Dep. Otorhinolaryngol., Univ. Liverpool, Royal Liverpool Hosp., PO Box 147, Liverpool L69 3BX, UK

Clinical Otolaryngology and Allied Sciences (Oxford) 19 (1). 1994. 63-69.

Full Journal Title: Clinical Otolaryngology and Allied Sciences (Oxford)

ISSN: 0307-7772

Language: ENGLISH

It would seem logical that patients with nodal metastases low in the neck would fare less well than patients with disease high in the neck. The penultimate UICC classification suggested that neck node level was important although there was no mention of this in the most recent classification. In addition, patients with carcinomas at the various sites would be expected to have different patterns of nodal involvement. Of 3419 patients with head and neck squamous carcinoma on the Liverpool University Head and Neck Unit database, 947 had neck node metastases. The neck node levels were coded as (I) sub-mandibular, (II) above the thyroid notch, (III) below the thyroid notch and (IV) supra-clavicular/posterior triangle nodes. Levels II and III contained the deep jugular chain. The relationship between node level and site and sub-site and survival were analysed with particular emphasis on multivariate methods. The 5-year survival for the whole group was 51% and survival fell with decreasing node level (I-IV) being 37% for sub-mandibular nodes, 32% for deep cervical nodes and 25% for lower deep cervical nodes. The 18-month survival for supra-clavicular and posterior triangle nodes was 21%. The difference in survival was significant ($\chi^2 = 24.42$, $P < 0.001$). Multivariate analysis confirmed that as the level of the nodes fell from the sub-mandibular region to the supra-clavicular region the prognosis worsened (estimate = -0.3378, $P = 0.0003$). Level II (upper deep cervical) nodes were the most commonly involved with regards to all primary sites and formed 69% of all neck node metastases. Over three quarters of laryngeal oropharyngeal and hypopharyngeal metastases went to this level whereas only 47% of oral cancers did. Most of the remainder of these latter lesions metastasized to level I (42%). These findings were confirmed by multiple logistic regression. When studying survival for lymph node level with regard to site all sites had a reducing prognosis with decreasing node level except for larynx. Multiple linear regression showed an association between decreasing node level and increasing N-stage ($P = 0.001$) with increasing T-stage ($P = 0.0014$) and as the site moved from the mouth to the larynx ($P = 0.0047$). The present data support the view that neck node level is important as regards prognosis for most sites in the head and neck. The data confirm the clinical view that deep cervical nodes are most frequently affected by head and neck cancer with level IV nodes being unusual and clinically tending to herald a non head and neck tumour and that level III nodes are relatively uncommon. This is surprising as one would expect at least a proportion of laryngeal carcinomas and quite a high proportion of hypopharyngeal carcinomas to metastasize to this region.

"thyroid notch"
not
notch
proteins

11/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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10514120 BIOSIS Number: 96114120

CLINICAL UNDERESTIMATION OF LARYNGEAL CANCER PREDICTIVE INDICATORS
NAKAYAMA M; BRANDENBURG J H
DIV. OTOLARYNGOL.-HEAD AND NECK SURG., DEP. SURG., UNIV.
WISCONSIN-MADISON, 600 HIGHLAND AVE., MADISON, WI 53792-3236, USA.
ARCH OTOLARYNGOL HEAD NECK SURG 119 (9). 1993. 950-957. CODEN: AONSE
Full Journal Title: Archives of Otolaryngology Head & Neck Surgery
Language: ENGLISH

Objective: To evaluate the accuracy of clinical staging of advanced laryngeal cancer and to morphologically analyze the underestimated cases. Design: We conducted a retrospective histopathologic study of larynges from patients who had total laryngectomy and were seen over a 21-year period. Setting: Academic tertiary referral medical center. Participants: Forty-one patients had clinically staged T3 laryngeal cancer and 16 patients had T4 cancer. Intervention: Patients all underwent wide-field total laryngectomy. All larynges were processed as whole-organ serial sections in the coronal plane. Outcome Measure: The incidence of clinically underestimated laryngeal cancer. During this investigation, it became obvious that predictive indicators of thyroid cartilage involvement could be established. Results: Clinical underestimation had been made in approximately 50% of all T3 laryngeal cancer cases. The extent of the cartilage involvement in the underestimated group was characterized by microinvasion without penetration; approximately 90% of the cartilage involvement affected the thyroid notch and adjacent area. We established five objective indicators of thyroid cartilage involvement: (1) extensive cartilage ossification (risk for cartilage involvement, 73%); (2) glottic fixation (54%); (3) transglottic cancer (74%); (4) tumor length longer than the entire vocal fold length or longer than 2 cm (66%); and (5) extensive involvement of the anterior commissure (67%). Conclusions: Clinical underestimation of T4 laryngeal cancer was high because thyroid cartilage involvement was not accurately diagnosed. We believe our indicators of thyroid cartilage involvement will provide objective guidelines for laryngeal cancer staging and will contribute to more reliable clinical cancer-staging decisions.

*thyroid
notch —
not
"notch proteins"*

11/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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6459256 BIOSIS Number: 85059777

CT-PATHOLOGIC CORRELATION IN SMALL PERIPHERAL LUNG CANCERS
KURIYAMA K; TATEISHI R; DOI O; KODAMA K; TATSUTA M; MATSUDA M; MITANI T;
NARUMI Y; FUJITA M
DEP. DIAGNOSTIC RADIOL., CENTER ADULT DISEASES, 3 NAKAMICHI, 1-CHOME,
HIGASHINARI-KU, OSAKA 537, JPN.
AJR (AM J ROENTGENOL) 149 (6). 1987. 1139-1143. CODEN: AJROA
Language: ENGLISH

To evaluate the morphology of small peripheral lung cancers, we studied thin-section CT images of 18 small peripheral lung cancers (14 adenocarcinomas, two squamous-cell carcinomas, one large-cell carcinoma,

and one carcinoid) in 17 patients. After surgical resection, specimens were sliced transversely, and the gross morphology and histology were correlated with the appearance of the lesion on preoperative thin-section CT images. CT images showed fine spiculations in 78%, a notch in 83%, pleural retraction in 78%, and convergence of peripheral vessels in 83% of the 18 lung cancers. Furthermore, in cases of papillary adenocarcinoma, the lesions had heterogeneous densities (78%) and small cavitations (67%). CT showed a peripheral fluffy zone in most of the well- or moderately differentiated papillary adenocarcinomas. This correlated well with tumor cells lining the alveolar walls, observed in pathologic studies. Comparison of thin-section CT images with pathologic data suggests that the demonstration of the lung-tumor interface and the tumor's internal texture, while not specific for malignant lesions, can make the CT diagnosis of small peripheral lung cancers more accurate.

"notch" used as morphological term

11/7/16 (Item 16 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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5370220 BIOSIS Number: 82015023
X-RAY MANIFESTATIONS OF ATYPICAL PERIPHERAL LUNG CANCER ANALYSIS OF 100 CASES

JI W; ET AL

SHANGHAI FIRST TUBERCULOSIS HOSP., SHANGHAI.

ZHONGHUA ZHONGLIU ZAZHI 7 (4). 1985 (RECD. 1986). 280-282. CODEN:

CCLCD

Full Journal Title: Zhonghua Zhongliu Zazhi

Language: CHINESE

The X-ray findings of 100 cases of atypical peripheral lung cancer as compared with those of their pathological specimens are reported. In the chest film, the lesions showed irregular mass shadows, flakes of infiltrations, scattered nodules, rod-like infiltrations, thickened lung markings and thin-walled cavities, etc. These atypical X-ray changes are due to the intermingling of (1) the site (2) the growth mode (3) the histologic type. For different lesions, even if the histologic type, position and size are the same, the X-ray findings may still be atypical due to the various growth modes. In addition to the recognition of the typical X-ray features, e.g. lobation, spicula, notch, etc. sputum exfoliative cytology, fibrobronchoscopic examination, puncture biopsy of the lung must also be considered in order to ensure early diagnosis.

11/7/17 (Item 17 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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5306560 BIOSIS Number: 81073867
BREAST CANCER METASTASIS TO INTRAMAMMARY LYMPH NODES
LINDFORS K K; KOPANS D B; MCCARTHY K A; KOERNER F C; MEYER J E
DEP. RADIOL., MASS. GEN. HOSP., BOSTON, MASS. 02114.
AJR (AM J ROENTGENOL) 146 (1). 1985. 133-136. CODEN: AJROA
Language: ENGLISH

Metastatic disease to the intramammary lymph nodes from breast cancer may be seen mammographically. In the four cases reviewed, the affected intramammary lymph nodes were enlarged (1 cm or greater in diameter),

homogeneous, and well circumscribed. All lacked the lucent center or hilar notch characteristic of benign intramammary nodes. Differentiation of malignant from benign causes of intramammary lymph node enlargement, such as inflammation or hyperplasia, is impossible by mammography. Biopsy is recommended for all intramammary lymph nodes of 1 cm or greater that are not fat infiltrated unless the patient clearly has an associated dermatitis or mastitis. Metastatic disease to the intramammary lymph nodes may be the first clinical and/or mammographic sign of breast cancer and may significantly affect prognosis.

11/7/29 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE
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8448577 EMBASE No: 92124741

Expression of an activated Notch-related int-3 transgene interferes with cell differentiation and induces neoplastic transformation in mammary and salivary glands

Jhappan C.; Gallahan D.; Stahle C.; Chu E.; Smith G.H.; Merlino G.; Callahan R.

USA

GENES DEV. (USA) , 1992, 6/3 (345-355) CODEN: GEDEE ISSN: 0890-9369

LANGUAGES: English SUMMARY LANGUAGES: English

Expression of the int-3 locus is activated in mouse mammary tumors as a consequence of insertional mutagenesis by the mouse mammary tumor virus (MMTV). Integration of the MMTV provirus into the int-3 locus promotes the transcription and translation of flanking cellular int-3 sequences sharing significant homology with the intracellular domain of the neurogenic Notch gene of *Drosophila*, and with the yeast cell cycle regulatory genes *cdc10* and *SWI6*. To determine the in vivo consequences of activated int-3 expression, transgenic mice were generated harboring a genomic tumor DNA fragment consisting of the MMTV LTR and the flanking cellular int-3 sequences. All six int-3 founder transgenic mice and the progeny of one established line exhibited similar dramatic phenotypic abnormalities in tissues in which the transgene was expressed. Focal and often multiple poorly differentiated mammary and salivary adenocarcinomas appeared in the majority of transgenic mice between 2 and 7 months of age. Significantly, mammary glands were arrested in development and were lactation deficient in all female int-3 mice. The salivary glands, glands of the nasal mucosa and maxillary sinus, the extraorbital lacrimal glands, and the Harderian glands of juvenile and adult transgenic mice all contained proliferating immature ductule cells and were incompletely differentiated. In addition, all male int-3 transgenic mice were sterile, apparently the result of severe hyperplasia of the epididymis. These findings demonstrate in vivo that expression of the activated Notch-related int-3 gene causes deregulation of normal developmental controls and hyperproliferation of glandular epithelia.

11/7/30 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE
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8238175 EMBASE No: 91266932

TAN-1, the human homolog of the *Drosophila* Notch gene, is broken by

chromosomal translocations in T lymphoblastic neoplasms

Ellisen L.W.; Bird J.; West D.C.; Soreng A.L.; Reynolds T.C.; Smith S.D.; Sklar J.

Stanford University School of Medicine, Stanford, CA 94305 USA

CELL (USA) , 1991, 66/4 (649-661) CODEN: CELLB ISSN: 0092-8674

LANGUAGES: English

Previously we described joining of DNA in the beta T cell receptor gene to DNA of an uncharacterized locus in a t(7;9)(q34;q34.3) chromosomal translocation from a case of human T lymphoblastic leukemia (T-ALL). We now show that the locus on chromosome 9 contains a gene highly homologous to the Drosophila gene Notch. Transcripts of the human gene, for which we propose the name TAN-1, and its murine counterpart are present in many normal human fetal and adult mouse tissues, but are most abundant in lymphoid tissues. In t(7;9)(q34;q34.3) translocations from three cases of T-ALL, the breakpoints occur within 100 bp of an intron in TAN-1, resulting in truncation of TAN-1 transcripts. These observations suggest that TAN-1 may be important for normal lymphocyte function and that alteration of TAN-1 may play a role in the pathogenesis of some T cell neoplasms.

?

17/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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11066516 BIOSIS Number: 97266516

Ep-CAM: A human epithelial antigen is a homophilic cell-cell adhesion molecule

Litvinov S V; Velders M P; Bakker H A M; Fleuren G J; Warnaar S O
Dep. Pathol., State Univ. Leiden, Wassenaarsweg 62, P.O. Box 9603, 2300
RC Leiden, NET

Journal of Cell Biology 125 (2). 1994. 437-446.

Full Journal Title: Journal of Cell Biology

ISSN: 0021-9525

Language: ENGLISH

The epithelial glycoprotein 40 (EGP40, also known as GA733-2, ESA, KSA, and the 17-1A antigen), encoded by the GA-733-2 gene, is expressed on the baso-lateral cell surface in most human simple epithelia. The protein is also expressed in the vast majority of carcinomas and has attracted attention as a tumor marker. The function of the protein is unknown. We demonstrate here that EGP40 is an epithelium-specific intercellular adhesion molecule. The molecule mediates, in a Ca-2+-independent manner, a homophilic cell-cell adhesion of murine cells transfected with the complete EGP40 cDNA. Two murine cell lines were tested for the effects of EGP40 expression: fibroblastic L cells and dedifferentiated mammary carcinoma L153S cells. The expression of the EGP40 protein causes morphological changes in cultures of transfected cells-increasing intercellular adhesion of the transfectants-and has a clear effect on cell aggregating behavior in suspension aggregation assays. EGP40 directs sorting in mixed cell populations, in particular, causes segregation of the transfectants from the corresponding parental cells. EGP40 expression suppresses invasive colony growth of L cells in EHS-matrigel providing tight adhesions between cells in growing colonies. EGP40 can thus be considered a new member of the intercellular adhesion molecules. In its biological behavior EGP40 resembles to some extent the molecules of the immunoglobulin superfamily of cell adhesion molecules (CAMs), although no immunoglobulin-like repeats are present in the EGP40 molecule. Certain structural similarities in general organization of the molecule exist between EGP40 and the lin-12/Notch proteins. A possible role of this adhesion molecule in formation of architecture of epithelial tissues is discussed. To reflect the function of the molecule the name Ep-CAM for EGP40 seems appropriate.

17/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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10110234 BIOSIS Number: 95110234

DLK A PUTATIVE MAMMALIAN HOMEOTIC GENE DIFFERENTIALLY EXPRESSED IN SMALL CELL LUNG CARCINOMA AND NEUROENDOCRINE TUMOR CELL LINE

LABORDA J; SAUSVILLE E A; HOFFMAN T; NOTARIO V
CENTER BIOL. RESEARCH, FDA., 8800 ROCKVILLE PIKE, BLDG. 29, BETHESDA, MD
20892, USA.

J BIOL CHEM 268 (6). 1993. 3817-3820. CODEN: JBCHA

Full Journal Title: Journal of Biological Chemistry

Language: ENGLISH

Gastrin releasing peptide is mitogenic for mouse Swiss 3T3 fibroblasts and certain human small cell lung carcinoma (SCLC) cells but not for mouse Balb/c 3T3 fibroblasts. To identify new molecules associated with the gastrin releasing peptide-responsive phenotype, clones isolated from a differential cDNA library between Swiss and Balb/c 3T3 fibroblasts were used to screen for their expression in human SCLC cell lines. Using this approach, we have isolated and characterized human and mouse cDNA clones encoding a novel protein. This protein is a putative transmembrane protein belonging to the epidermal growth factor-like superfamily. In vitro transcription and translation studies detect a 42-kDa protein, in agreement with the size predicted from the translated cDNA sequence. This protein (termed Delta-like or dlk) is highly homologous to invertebrate homeotic proteins, including Delta, and Notch, the products of neurogenic loci involved in normal neural differentiation in *Drosophila*. dlk is expressed in tumors with neuroendocrine features, such as neuroblastoma, pheochromocytoma, and a subset of SCLC cell lines. However, its expression in normal tissues is restricted to the adrenal gland and placenta. These data suggest that dlk may be involved in neuroendocrine differentiation and, because of its cellular location and restricted expression in normal tissues, it may be a potential therapeutic target in neuroendocrine tumors, particularly SCLC.

17/7/3 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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07828367 91347367

TAN-1, the human homolog of the *Drosophila* notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms.

Ellisen LW; Bird J; West DC; Soreng AL; Reynolds TC; Smith SD; Sklar J
Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts 02115.

Cell (UNITED STATES) Aug 23 1991, 66 (4) p649-61, ISSN 0092-8674
Journal Code: CQ4

Contract/Grant No.: CA38621, CA, NCI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Previously we described joining of DNA in the beta T cell receptor gene to DNA of an uncharacterized locus in a t(7;9)(q34;q34.3) chromosomal translocation from a case of human T lymphoblastic leukemia (T-ALL). We now show that the locus on chromosome 9 contains a gene highly homologous to the *Drosophila* gene Notch. Transcripts of the human gene, for which we propose the name TAN-1, and its murine counterpart are present in many normal human fetal and adult mouse tissues, but are most abundant in lymphoid tissues. In t(7;9)(q34;q34.3) translocations from three cases of T-ALL, the breakpoints occur within 100 bp of an intron in TAN-1, resulting in truncation of TAN-1 transcripts. These observations suggest that TAN-1 may be important for normal lymphocyte function and that alteration of TAN-1 may play a role in the pathogenesis of some T cell neoplasms.

17/7/4 (Item 1 from file: 434)

DIALOG(R)File 434:SciSearch(R)

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12891144 Genuine Article#: BZ51X Number of References: 95
Title: FREQUENT MUTATIONS IN BREAST-CANCER
Author(s): CALLAHAN R; GALLAHAN D; SMITH G; CROFF C; MERLO G; DIELLA F;
 LISCIA D; LIDEREAU R
Corporate Source: NCI,BLDG 10,ROOM 5B50/BETHESDA//MD/20892; SAN GIOVANNI
 VECCHIO HOSP,USSL 1,PATHOL SECT/I-10123 TURIN//ITALY//; CTR RENE
 HUGUENIN/ST CLOUD//FRANCE/
Journal: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 1993, V698, P21-30
ISSN: 0077-8923
Language: ENGLISH Document Type: ARTICLE

17/7/5 (Item 2 from file: 434)
DIALOG(R)File 434:SciSearch(R)
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11736855 Genuine Article#: JG755 Number of References: 74
Title: EXPRESSION PATTERN OF MOTCH, A MOUSE HOMOLOG OF DROSOPHILA-NOTCH,
 SUGGESTS AN IMPORTANT ROLE IN EARLY POSTIMPLANTATION MOUSE DEVELOPMENT
Author(s): DELAMO FF; SMITH DE; SWIATEK PJ; GENDRONMAGUIRE M; GREENSPAN RJ;
 MCMAHON AP; GRIDLEY T
Corporate Source: ROCHE INST MOLEC BIOL,ROCHE RES CTR,DEPT CELL &DEV
 BIOL/NUTLEY//NJ/07110; ROCHE INST MOLEC BIOL,ROCHE RES CTR,DEPT CELL
 &DEV BIOL/NUTLEY//NJ/07110; ROCHE INST MOLEC BIOL,ROCHE RES CTR,DEPT
 NEUROSCI/NUTLEY//NJ/07110
Journal: DEVELOPMENT, 1992, V115, N3 (JUL), P737&
Language: ENGLISH Document Type: ARTICLE

Abstract: The Notch gene of Drosophila encodes a large transmembrane protein involved in cell-cell interactions and cell fate decisions in the Drosophila embryo. To determine if a gene homologous to Drosophila Notch plays a role in early mouse development, we screened a mouse embryo cDNA library with probes from the Xenopus Notch homolog, Xotch. A partial cDNA clone encoding the mouse Notch homolog, which we have termed Motch, was used to analyze expression of the Motch gene. Motch transcripts were detected in a wide variety of adult tissues, which included derivatives of all three germ layers. Differentiation of P19 embryonal carcinoma cells into neuronal cell types resulted in increased expression of Motch RNA. In the postimplantation mouse embryo Motch transcripts were first detected in mesoderm at 7.5 days post coitum (dpc). By 8.5 dpc, transcript levels were highest in presomitic mesoderm, mesenchyme and endothelial cells, while much lower levels were detected in neuroepithelium. In contrast, at 9.5 dpc, neuroepithelium was a major site of Motch expression. Transcripts were also abundant in cell types derived from neural crest. These data suggest that the Motch gene plays multiple roles in patterning and differentiation of the early postimplantation mouse embryo.

17/7/6 (Item 1 from file: 442)
DIALOG(R)File 442:AMA Journals Online
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00086699
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Continuing Trends in the Prevalence of Right-Sided Lesions Among Colorectal Carcinomas (ARTICLE)

CADY, BLAKE; STONE, MICHAEL D.; WAYNE, JEFFREY
Archives of Surgery
May, 1993; Paper: p505
LINE COUNT: 00444
0004-0010

The shift of colorectal carcinoma location toward the proximal colon has been reported. This study documents that this statistically significant trend has continued through 1992. An increase in transverse and descending colon cancers is now apparent also. Only 59% of all large-bowel cancers occurred distal to the descending colon between 1978 and 1992. Both right-sided and distal large-bowel cancers have significantly decreased in size, yet the incidence and frequency of lymph node metastases have not changed over a 65-year interval (from 1928 to 1992). This constant proportion of lymph node metastases may suggest distinct biological subsets of cancers (lymph node avid vs lymph node avoidance). The progression from small size with fewer metastases to large size with more lymph node metastases occurs only in some of the smallest distal colorectal cancers.

* * USE FORMAT 9 FOR FULL TEXT OF ARTICLE * *

17/7/7 (Item 2 from file: 442)
DIALOG(R)File 442:AMA Journals Online
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00052296

Mandible Reconstruction With Vascularized Bone Grafts: A Histologic Evaluation (Article)

Hoffman, Henry T., MD; Harrison, Nancy, MD; Sullivan, Michael J., MD; Robbins, K. Thomas, MD; Ridley, Marion, MD; Baker, Shan R., MD
Archives of Otolaryngology-Head & Neck Surgery
1991; 117: 917 (9)
0003-9977

To our knowledge, a histologic evaluation of bone healing after mandible reconstruction with vascularized human bone grafts has not been previously reported. Serial sections through both the decalcified graft and the junction between mandible and graft were evaluated in four patients who required surgical removal of their reconstructed mandibles. A failed scapular bone graft that had been wrapped within a pectoralis major myocutaneous flap for salvage following pedicle thrombosis showed markedly resorbed but viable bone with a fibrous union to the native mandible. Viable vascularized grafts without evidence of ongoing resorption characterized an iliac osteocutaneous bone graft and two scapula osteocutaneous grafts that healed with continuity of healthy bone between graft and mandible. Observations from the evaluation of these specimens are made regarding bone circulation, bone union, and bone graft survival as they occur clinically. Implications regarding the techniques of bone plating and indications for use of vascularized bone in mandible reconstruction are discussed.

* * USE FORMAT 9 FOR FULL TEXT OF ARTICLE * *

17/7/8 (Item 3 from file: 442)
DIALOG(R)File 442:AMA Journals Online
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00050946

Null Cell Adenoma of the Pituitary With Features of Plurihormonality and
Plurimorphous Differentiation (Article)

Kontogeorgos, George, MD; Horvath, Eva, PhD; Kovacs, Kalman, MD, PhD;
Killinger, Donald W., MD, PhD; Smyth, Harley S., MD, PhD
Archives of Pathology & Laboratory Medicine
1991; 115: 61 (4)
0363-0153

The case of a 35-year-old man with pituitary macroadenoma who was complaining of reduced sexual activity is presented. Histologic examination showed a chromophobic adenoma corresponding mainly to a null cell adenoma at the ultrastructural level. Focal plurihormonality and plurimorphous differentiation of adenoma cells were demonstrated by immunohistochemical and electron-microscopic studies. It is suggested that adenomatous null cells represent pluripotent progenitor cells capable of transforming to different hormone-producing cell types. The factors accounting for differentiating to various cell populations have yet to be elucidated.

* * USE FORMAT 9 FOR FULL TEXT OF ARTICLE * *

17/7/9 (Item 4 from file: 442)
DIALOG(R)File 442:AMA Journals Online
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00040033

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Markers of Thrombotic Activity in Arterial Disease (PAPERS READ BEFORE THE
13TH ANNUAL MEETING OF THE NEW ENGLAND SOCIETY FOR VASCULAR SURGERY
DIXVILLE NOTCH, NH, SEPT 25 TO SEPT 26, 1986)

DONALDSON, MAGRUDER C.; MATTHEWS, EILEEN T.; HADJIMICHAEL, JANE; RICKLES,
FREDERICK R.

Archives of Surgery
August, 1987; 122: 897-900

LINE COUNT: 00187 WORD COUNT: 02593

ISSN: 0004-0010

CORPORATE SOURCE: Accepted for publication March 13, 1987. From the Departments of Surgery (Dr Donaldson and Ms Hadjimichael) and Hematology/Oncology (Ms Matthews and Dr Rickles), University of Connecticut School of Medicine, Farmington. Dr Donaldson is now with the Department of Surgery, Brigham and Women's Hospital, Boston. Read before the 13th Annual Meeting of the New England Society for Vascular Surgery, Dixville Notch, NH, Sept 26, 1986. Reprint requests to Department of Surgery, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (Dr Donaldson). This study was supported in part by the Medical Research Service of the Veterans Administration and by grants-in-aid from the American Heart Association and

its Connecticut affiliate, Meriden (AHA 83-957); Department of Health and Human Services, Washington, DC (CA 22202); and the American Cancer Society, New York (CH 321). The authors thank Margaret Peterson, PhD, for assistance in data processing and analysis.

ABSTRACT: Levels of the platelet degranulation product beta-thromboglobulin (BTG) and the fibrinogen degradation product fibrinopeptide A (FPA) were measured in 26 asymptomatic subjects (group 1), 17 patients with peripheral vascular disease (PVD) (group 2), and 12 patients with PVD and bypass grafts (group 3). Mean BTG and FPA levels were elevated in both groups 2 and 3, indicating increased thrombotic activity in patients with PVD. Results of serial BTG and FPA assays in group 3 patients suggested a trend downward. These markers may be useful for estimating disease severity and prognosis, extent of graft healing and patency, and efficacy of therapeutic intervention.

* * USE FORMAT 9 FOR FULL TEXT OF ARTICLE * *

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drugs in coronary artery disease. Circulation Discussion

DR CRONENWETT, Hanover, NH: Since many factors may influence BTG levels (including age, diabetes, smoking, and hyperlipidemia), what was the basis for the difference observed in this study between normal subjects (group 1) and patients with PVD (groups 2 and 3)? Since the range of BTG levels in these groups demonstrated some overlap, are the tests best suited to follow individual patients for sequential comparisons? Do measurements of PF4 rule out in vitro activation of platelets and artifactual BTG release? Do platelet counts in the patients influence results? Have you had an opportunity to study the same patient before and after the administration of antiplatelet medication to determine the potential usefulness of these assays to monitor therapy? I think this is an important initial step in the characterization of thrombotic problems in these patients.

DR HUME, Boston: Is there any variation in these tests associated with age?

DR DONOVAN, Hartford, Conn: Have you noticed any difference in the axillobifemoral grafts where you have a broad surface exposed to the blood?

DR DONALDSON: The findings of elevations in BTG and FPA in various kinds of vascular disease are not new. The questions reflect the difficulties with these assays. There are difficulties in standardizing the assays, which I think we have accomplished, and then in trying to sort out the many risk factors that go along with arterial disease as independent variables. Diabetes, hypertension, and hyperlipidemia may exert their influence on these markers through their effect on arteries rather than independently.

Platelet factor 4 is another platelet-specific alpha granule constituent. It has a short half-life compared with BTG because much of the PF4 that is released in vivo becomes adherent to the endothelial wall. It has been suggested that PF4 be measured along with BTG with the idea that, if relative levels of PF4 are equal to or greater than BTG, there has been in vitro alpha granule release. We have started to assay PF4 and are satisfied that PF4 levels were low in the patients we have looked at.

In the literature, platelet counts have sometimes been associated with higher levels of BTG, PF4, and FPA. It is not clear whether the count is an important aspect. We measured platelet counts as part of this study and found that there was not a significant difference among the groups.

We have started a trial using aspirin just to see if it is associated with decreased levels of BTG. Again, the literature is not clear on this point.

The age in the control group was generally younger. Some of these patients were from a pool used by our hematology laboratory, and though age has been associated with elevations as an apparently independent factor, I venture to say that measurement of age is really a measurement of underlying preclinical arterial disease. Our initial thought was that graft surfaces would put this idea to the test because they would stress the thrombotic system, so we chose axillobifemoral grafts, thinking that the larger surface area would give us the biggest difference between normal and abnormal levels of thrombotic markers.

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00039942

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Monoclonal Antibody-Mediated Modulation of Parathyroid Hormone Secretion by
Dispersed Parathyroid Cells (PAPERS READ BEFORE THE 67TH ANNUAL MEETING OF
THE NEW ENGLAND SURGICAL SOCIETY DIXVILLE NOTCH, NH, SEPT 26-28, 1986)

POSILLICO, JAMES T.; WILSON, RICHARD E.; SRIKANTA, SRI S.; EISENBARTH,
GEORGE S.; LETARTE, MICHELLE; QUACKENBUSH, ELIZABETH J.; QUARANTA, VITO;
KAJAJI, SHANA; BROWN, EDWARD M.

Archives of Surgery

April, 1987; 122: 436-442

LINE COUNT: 00312

WORD COUNT: 04319

ISSN: 0004-0010

CORPORATE SOURCE: Accepted for publication Dec 30, 1986. From the
Departments of Medicine (Drs Posillico and Brown) and Surgery (Dr Wilson),
Brigham and Women's Hospital and Harvard Medical School, Boston; Department
of Medicine, Joslin Diabetes Center and Harvard Medical School, Boston (Drs
Srikanta and Eisenbarth); Department of Immunology, The Hospital for Sick
Children, Toronto (Drs Letarte and Quackenbush); and Department of
Immunology, Scripps Clinic and Research Foundation, La Jolla, Calif (Drs
Quaranta and Kajaji). Read before the 67th Annual Meeting of the New
England Surgical Society, Dixville Notch, NH, Sept 27, 1986. Reprint
requests to Endocrine-Hypertension Unit, Department of Medicine, Brigham
and Women's Hospital, 75 Francis St, Boston, MA 02115 (Dr Posillico). This
investigation was supported in part by National Institutes of Health,
Bethesda, Md, grants AM36801 and AM36796 and by the Brigham Surgical Group
Foundation Inc, Boston. Antibody CK-13, which was used in the
radioimmunoassay, was donated by G. V. Segre, MD, of Massachusetts General
Hospital, Boston.

ABSTRACT: Available data suggest that ionized calcium may interact with a
cell surface "sensor" or "receptor" to produce changes in one or more
intracellular second messengers that ultimately regulate the release of
parathyroid hormone (PTH). Recently, we developed a series of monoclonal
antibodies directed toward specialized differentiation antigens expressed
on endocrine cells. Since many of these monoclonal antibodies displayed
exquisite specificity for cell surface molecules on the parathyroid cell,
we used these reagents as probes to investigate signal
recognition/transduction mechanisms associated with abnormal
calcium-regulated PTH secretion. Depending on their binding site on the
respective target antigen molecules, these monoclonal antibodies either
stimulated or inhibited hormone secretion. Thus, defects in
membrane-associated structures may contribute to deranged calcium-regulated
PTH secretion in abnormal parathyroid cells.

* * USE FORMAT 9 FOR FULL TEXT OF ARTICLE * *

CITED REFERENCES:

Discussion

ROGER S. FOSTER, JR, MD, Burlington, Vt: Is the abnormal parathyroid
response to the level of external calcium an intrinsic property of
parathyroid tissue in hyperparathyroidism? Is it an example of cause
and effect or of down-regulation related to chronic exposure to high
levels of ionized calcium?

Some years ago, a series of rodent experiments was conducted in which multiple normal glands were transplanted to increase parathyroid mass. For a period of time, the blood level of calcium was elevated, so it took a while for down-regulation to occur. One approach might be to study normal glands, perhaps obtained at autopsy, in patients with malignant hypercalcemia to see whether these glands would respond like the pathologic glands in the present study.

BARBARA K. KINDER, MD, New Haven, Conn: I would like to persuade you that the present study's subject, namely, the regulation of hormone secretion by calcium fluxes across cell membranes, is really fundamental to our understanding of how a variety of different cells work. All cells maintain a very low cytosolic or intracellular free calcium concentration, in fact, a ten-thousandth of that which exists outside the cell.

The existence of this calcium gradient across the cell membrane permits calcium to serve as an intracellular second messenger in a variety of cell functions when the cell is stimulated by hormonal, chemical, or electrical impulses. The signal mediated by calcium is then terminated by removal of calcium from the cytosolic compartment by a variety of different calcium pumps. One of the calcium pumps present probably in all cell surface membranes is the sodium-calcium exchanger. Two of the monoclonal antibodies used in this study, the 4F2 and the 44D7, have been shown in other systems to probably be directed against either the sodium-calcium exchanger itself or its close regulator.

The authors present data showing that treatment with monoclonal antibodies causes adenomatous parathyroid cells to respond more like normal cells. These results are very intriguing and raise many possibilities for therapeutic use.

I would like to know whether the authors have characterized the effects of the monoclonal antibody in normal parathyroid cells. I would also like to tempt the authors to speculate on what this study might tell us about the biochemical abnormality in adenomatous and, presumably, hyperplastic parathyroid cells. It seems that there could be two explanations. First, there could be too many sodium-calcium channels expressed on the surface of abnormal parathyroid cells. When you treat the cells with monoclonal antibody, it blocks some of these channels; calcium can then rise because it is not being pumped out all the time, and hormone secretion is inhibited. On the other hand, the sodium-calcium channel is known to be bidirectional, and it may be that there are too few working units in the pathologic cell. The presence of monoclonal antibody could activate these units or allow them to become more effective. One way to discriminate between calcium being pumped in or out of the cell would be to use radioactive calcium loading and washout studies. Have you attempted either of these procedures?

Finally, the authors and their group have been largely responsible for our understanding of how PTH secretion is regulated and have long had an interest in the role of cyclic nucleotides in the regulation of that secretion. I would be interested to know how they relate these data about the cell surface markers to intracellular regulation, and whether they see a role for calcium-regulated second messenger systems, such as the protein kinase C system and cyclic calcium calmodulin-dependent protein kinase systems.

DR WILSON: Normal cells do not seem to respond in the way that adenoma cells do to monoclonal antibodies. Membrane fixation of monoclonal

antibodies to alter PTH secretion appears to be a property of the diseased cell. I would agree that it is not just a membrane transfer reaction; protein kinase, cyclic nucleotide, or some other complex intracellular mechanism is required to alter PTH secretion.

We do use Quin-2 to study concentrations of intracellular free calcium. Dr Brown has studied calmodulin recently, but apparently this system could not explain these differences in cell behavior.

We reported studying normal parathyroid glands from patients who had adenomas. The set point (50% maximum reduction in PTH secretion) is much lower in cells from normal glands of patients with adenomas than it is from normal glands studied on parathyroid biopsy specimens taken during thyroidectomy. Therefore, the effect of a high concentration of calcium should eventually reduce the PTH secretion in these rodent transplants. I believe that the cell surface membrane is adequately well regulated to protect the parathyroid cell from major fluxes in ionized calcium. I would like to stress, as Dr Kinder pointed out, that calcium is really becoming one of the most important ions in the study of both normal and abnormal physiology.

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Adjunct Hyperbaric Oxygen Therapy in Periorbital Reconstruction (SURGICAL TECHNIQUES)

GONNERING, RUSSELL S.; KINDWALL, ERIC P.; GOLDMANN, ROBERT W.

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ABSTRACT: The abundant blood supply normally found in the periorbital region grants the reconstructive surgeon many options for repair. When this blood supply is altered by such factors as thermal damage or scar formation, classic methods of lid reconstruction may not suffice. In such situations, treatment with hyperbaric oxygen accelerate the process of primary revascularization of full-thickness skin grafts and large composite grafts. Augmentation of capillary budding occurs because hyperbaric oxygen therapy raises the tissue oxygen tension in hypoxic areas to the level needed for extracellular deposition of collagen, which is needed for support of endothelial cells. Hyperbaric oxygen also appears to improve the survival of ischemic skin flaps of the face, although the exact mechanism of this action is unclear. Since 1982, a total of six patients needing

periorbital reconstruction has been treated postoperatively with adjunct hyperbaric oxygen. Although the results have been uniformly favorable, a matched series comparing the results with and without hyperbaric oxygen therapy will be required to prove the efficacy of this treatment regimen.

* * USE FORMAT 9 FOR FULL TEXT OF ARTICLE * *

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Recurrence of Acromegaly After Pituitary Apoplexy (BRIEF REPORTS)

WERNER, PHILIP L.; SHAH, JAYENDRA H.; KUKREJA, SUBHASH C.; MILLER, SCOTT M.; WILLIAMS, GERALD A.

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ABSTRACT: A 62-year-old woman with a history of acromegaly and an episode of pituitary apoplexy 18 years previously with subsequent biochemical and clinical inactivity of her acromegaly experienced a recurrence of active disease. Endocrine evaluation led to the discovery of hypopituitarism in association with hypersecretion of growth hormone. Patients with acromegaly and an episode of pituitary apoplexy with resultant inactive disease require long-term follow-up for the possibility of recurrence of active acromegaly.

* * USE FORMAT 9 FOR FULL TEXT OF ARTICLE * *

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Mechanisms of Disease: The Molecular Basis Of Leukemia (Review Articles)

Cline, Martin J.

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Weller, Peter F.; Gang, David L.

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